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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/522,030	03/09/00	THOMSON J	96-0296-9654

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HM12/1003

EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	5

DATE MAILED: 10/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/522,030	THOMSON, JAMES A	
	Examiner	Art Unit	
	Joseph Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is an original application filed March 9, 2000.

Claims 1-16 are pending and currently under examination.

Information Disclosure Statement

The information disclosure statement filed March 9, 2000 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Specifically, the Ornitz *et al.* reference was not considered because a copy of the reference was not supplied.

Specification

The use of the trademark KNOCKOUT SR has been noted in this application (page 6; line 22). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of culturing a primate and human pluripotent embryonic stem cell and deriving cells and cell lines therefrom, does not reasonably provide enablement for primate and human embryonic stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

The basis of the instant rejection focuses on the breadth of the claim and the requirement of the existence of primate and human embryonic stem cells. The specification does not specifically define an embryonic stem cell however, the present art accepted definition of an embryonic stem cell is a totipotent cell capable of contributing to all tissues of an animal including the germ cells (Nichols *et al.*, page 1341; first paragraph). The specification teaches that pluripotential primate and human stem cells have been previously described (page 1; first paragraph), and that the instantly claimed methods can be used for culturing said cells (page 6; lines 15-24). It is noted that the specification indicates again that the embryonic stem cells are

pluripotent (page 6; line 24), however because of the interchanging use of embryonic stem cell and pluripotential embryonic stem cell in the specification, the claims are being interpreted in the greatest reasonable breadth in light of the art accepted definition of a totipotent embryonic stem cell.

Claims 1-13 are drawn to a method for culturing embryonic stem cells. Claim 14 is drawn to the culture system used in said methods and claims 15 and 16 are drawn to cell line derived by said method. Claims 14-16 are included in the rejection with respect to the intended use and ability of the culture system to culture embryonic stem cells, and the ability of the culturing methods to obtain a embryonic stem cell line representing a totipotent embryonic cell. The specification teaches that the instantly claimed methods represent an improved method for isolating embryonic stem cells and discusses the ability to derive embryonic stem cell lines by said method. Again, the general characteristics attributed to the isolated and cultured stem cells may be reasonably interpreted as totipotent embryonic stem cells. The specification teaches that the primate and human embryonic cells and cell lines were isolated by methods previously described and used for non human primates and teaches that the cell lines are capable of differentiating into cells derived from all the three embryonic germ layers as evidenced by forming teratomas after injection into SCID mice and in vitro analysis of cells grown to confluence. However, there is no indication that the cell lines or cells derived from the cell lines are totipotent and capable of contributing to the germ cell.

The state of the art of the claimed invention is not very well established and very few species of animal have had a totipotent embryonic stem cell isolated. Further, the art of isolating embryonic stem cells is highly unpredictable. With regard to a developing embryo, Cruz *et al.* list some of the differences in early embryonic development among swine, oxen, horses, goats and sheep (page 166; Table 1). In addition, Piedrahita *et al.* teach that culturing and isolation conditions for one species may not be suitable for culturing and isolation of embryonic stem-like cells from anther species. Specifically, conditions that allowed production of porcine embryonic stem-like cells did not allow development of ovine embryonic stem-like cells (summarized on page 886; Table 1). Therefore, it would be recognized by one of skill in the art that one cannot simply extrapolate from procedures shown effective in one species to use or develop procedures for another species. As taught and demonstrated in Cruz *et al.* and Piedrahita *et al.* numerous attempts to isolate embryonic stem cells from species other than the mouse have been attempted however, demonstration that these cells are able to contribute to the germ line is awaited (summarized by Clark *et al.* page 250; second paragraph).

The specification sets forth procedures for the isolation of primate embryonic stem cells (US Patent 5,843,780 incorporated by reference), however, with respect to the human embryonic stem cells isolated by this procedure it has been shown to be successful only as far as the demonstration of certain markers, expression of chorionic gonadotropin and differentiation into cells representative of each of the three embryonic germ layers when injected into SCID mice. The specific examples provided in US Patent 5,843,780 demonstrate that pluripotent rhesus and

marmoset embryonic stem cells can be isolated, however, there is no indication that these monkey embryonic stem cells can contribute to the germline, nor is there a nexus between the methods used to isolate the monkey embryonic stem cells and there effectiveness for use in isolating human embryonic stem cells. In the absence of evidence that the methods for the isolation of monkey embryonic stem cells, produce true totipotent embryonic stem cells, the amount of experimentation required to carry out the methods for the isolation of human embryonic stem cells is paramount. Further, the amount of experimentation require to demonstrate that embryonic stem-like cells are true embryonic stem cells is great because the embryonic stem-like cells would require implantation into a blastocyst, growth to term, and demonstration that the mosaicism extends to all tissues including the germ cells.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and confusing because the antecedent basis of 'the stem cells' in line 3 is unclear. The lack of definition for the source and the nature of the cells being cultured makes the claim unclear because there are various types of stem cells; i.e hematopoietic stem cells, tissue specific stem cells, adult stem cells, and two types of embryonic stem cells, pluripotent and totipotent. It is unclear if the cell in line 3 are embryonic stem cells or if the culturing conditions of any type of stem cell under the claimed conditions will result in the generation of an embryonic stem cell. Further, in light of claim 3, the claim is unclear to whether a feeder layer is included in the culture conditions of claim 1, or if the claim intends to exclude FGF from a source other than just fibroblasts. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

Claims 1, 2, 9 and 10 are vague and indefinite in the recitation of 'essentially free of" mammalian fetal serum/any animal serum because the metes and bounds of essentially free are not clearly defined in the claim nor the specification. The specification provides guidance for conditions which are serum free (page 6; line 5-19), however it is not clear from the teachings in the specification what amount of serum could be present in a media and still be considered essentially serum free. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

Claims 15 and 16 are vague, unclear and indefinite in the recitation a 'cell line derived' because "derived" as defined in the instant specification 'is used in its broadest sense to cover directly or indirectly derived lines' (instant specification, page 5; lines 16-20). The verb 'derived'

as defined in Merriam Webster Dictionary is a transitive verb which encompasses 'derivation', that is a changing or modification of the parent or starting material. It is unclear how different the cultured cell can be and still be considered derived from primate embryonic stem cell. For example, from the specification it is clear that the cell lines H9.1 and H9.2 maintain normal XX karyotype and the ability to differentiate into all three germ layers after culture in serum-free medium (instant specification pages 8-9) and thus, have phenotypic characteristics of human pluripotent stem cells. However, it is unclear if the cell lines and cells derived from these cells only have and only maintain these defined characteristics or if they obtain further characteristics, even characteristics of differentiated cells. The claims are indefinite because the metes and bounds of the characteristics and phenotypes of the claimed 'derived' cell lines are not clearly defined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson *et al.* (IDS reference; Science 282:1145-1147).

Claims 15 and 16 are drawn to a cell line derived from the methods recited in claims 1 and 9. There are no specific characteristics of the cell line defined in the instant claims, and in light of the specification, the embryonic stem cells contemplated by the specification are capable of differentiating into many different cell types. In the broadest reasonable interpretation of a 'cell line derived', any primate or human cell line would anticipate the instantly claimed cell line. Further, because of issues concerning the recitation of 'derived' raised in the 35 USC 112, second paragraph, rejection, it is noted that patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thomson *et al.* teach two cell lines: H1 which has a normal XY karyotype and H9 which has a normal XX karyotype (page 1145; second column). Thomson *et al.* teach that when the cell lines are injected into an immunodeficient mouse the cell lines can differentiate into endoderm, mesoderm and ectoderm cell types (page 1146; middle of first column and page 1147; figure 4). It appears that the H-9 cultures are specifically taught in the instant specification (page 6; starting on line 25). Since the present methods represent an improved method of culturing embryonic stem cells, and there is no indication in the specification that the cells derived using the methodology instantly disclosed are different from cells cultured in other conditions, any

embryonic stem cell line would anticipate the instant claims. Thus, the cell lines H1 and H9 taught by Thomson *et al.* anticipate the claims.

Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson *et al.* (PNAS 92:7844-7848).

Claims 15 and 16 are summarized above. Thomson *et al.* describe primate embryonic stem cell lines which contain specific cell surface markers and are capable of differentiating into the cell types represented in the three germ layers of an embryo. In view of the teachings of the instant specification, where the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Thus, the cell lines taught by Thomson *et al.* anticipate the claims.

Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Damjanov *et al.* (Lab. Invest. 68:220-232).

As noted above, claims 15 and 16 can be reasonably interpreted as drawn to a cell capable of differentiated cell is selected from the group consisting of endodermal cell, mesodermal cell, and ectodermal cell. Damjanov *et al.* teach the human germ cell line NCCIT. In the characterization of the NCCIT cell line Damjanov *et al.* demonstrate that the cell line can differentiate into all three embryonic germ layers, ectoderm, mesoderm and endoderm (summarized on page 220, abstract and detailed section on immunochemistry pages 222-224). While the differentiated cells disclosed in Damjanov *et al.* are not specifically cultured by the methods disclosed in the instant application, a differentiated human cell line as claimed would be indistinguishable from those disclosed in Damjanov *et al.* Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson (US Patent 5,843,780), Hogan (US Patent 5,690,926), or Hogan (US Patent 5,670,372).

Claims 15 and 16 are summarized above. The patents by Thomson (US Patent 5,843,780), Hogan (US Patent 5,690,926), and Hogan (US Patent 5,670,372) each teach methodology for obtaining embryonic stem cells. Specifically, Thomson (US Patent 5,843,780) teach the isolation of primate embryonic stem cells, and Hogan (US Patent 5,690,926 and US Patent 5,670,372) teach the isolation of non-murine embryonic stem cells. Many of the

characteristic markers for an embryonic stem cell line are maintained by the isolated cell lines such as specific cell surface markers and the ability to differentiate into the three germ cell layers. Thus, each of the three patents teach cell lines which anticipate the instant claims.

Claims 15 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Thomson (US Patent 6,200,806) or Gerhart *et al.* (US Patent 6,245,566).

Claims 15 and 16 are summarized above. The patents by Thomson (US Patent 6,200,806) or Gerhart *et al.* (US Patent 6,245,566) each teach methodology for obtaining embryonic stem cells. Specifically, Thomson (US Patent 6,200,806) teaches the isolation of human pluripotent embryonic stem cells, and Gerhart *et al.* (US Patent 6,245,566) teach the isolation of human primordial germ cells. Many of the characteristic markers for the cells which are isolated maintain the specific cell surface markers and the ability to differentiate into the three germ cell layers. Thus, each Thomson and Gerhart *et al.* teach cells which anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan *et al.* (US Patent 5,670,372) , Hogan *et al.* (US Patent 5,690,926), and Goldsborough *et al.* (FOCUS 20(1):8-12, 1998).

Claims 1-13 are drawn to methods for culturing primate and human embryonic stem cells comprising culturing the stem cells in a medium essentially free of serum and in the presence of a supplemental source of fibroblast growth factor (FGF). Dependent claims recite that the culturing conditions must maintain specific cell characteristics such as a stable karyotype (note not necessarily normal karyotype) and the ability to differentiate in cells representing the three germ layers. Claims 14 is drawn to a cell culture system comprising a fibroblast feeder layer, supplemental source of fibroblast growth factor, and a medium which is essentially free of animal serum. Claims 15 and 16 are summarized above, and are included in this rejection because each of the references anticipates a cell line as instantly claimed for the reasons set forth above. Each reference of Hogan *et al.* teach the methods and culturing conditions for the isolation of a non-murine pluripotential cell. The cells which are isolated are maintained on feeder cell layers and supplemented with various growth factors including FGF. Further, the isolated cells maintain the ability to differentiate in embroid bodies representing the three germ cell layers (teaching throughout each of the patents and specifically claimed in 5,690,926). Further, patent 5,670,372 details culturing steps for identify the necessary factors needed to isolating, culturing and maintaining embryonic stem cells (specifically claimed). The combined teachings of Hogan *et al.* provide the necessary guidance for the artisan to isolate embryonic stem cells and optimize the

culturing conditions for various species of animals, and as specifically claimed in 5,690,926, for human pluripotential cells. However, the media in both Hogan *et al.* references the media used to culture the isolated cells contain serum. Goldsborough *et al.* teach serum free culturing conditions for embryonic stem cells. Specifically, Goldsborough *et al.* teach that use of the media Knockout SR (also used in the instant specification page 6; line 22) results in a greater number of undifferentiated colonies as compared to media containing serum. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to use the media taught by Goldsborough *et al.* in the methods taught by Hogan *et al.* for the isolation and maintenance of embryonic stem cells. One of ordinary skill in the art would have been motivated to combine the teachings of both Hogan *et al.* and Goldsborough *et al.* because of the specific teaching and general guidance by Hogan *et al.* that cell culturing conditions must be optimized for embryonic stem cells from species to species from which they are obtained, and the notable increased efficiency in use of Knockout SR media taught in Goldsborough *et al.* There would have been a reasonable expectation of success considering the skill in the art at the time of the claimed invention and the specific teachings and successful results of each Hogan *et al.* and Goldsborough *et al.* for the culturing of pluripotential embryonic stem cells.

Thus, the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is 1 (800)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800

Joseph T. Woitach